Survival Benefit Conferred by Topical Antimicrobial Preparations in Burn Patients: A Historical Perspective

Timothy P. La H. Brown, M Chir, FRCS (Plast), RAMC (v), Leopoldo C. Cancio, MD, FACS, LTC, MC, US Army, Albert T. McManus, PhD, and Arthur D. Mason, Jr., MD

Background: **Topical antimicrobial agents have proven efficacy in preventing life-threatening invasive burn wound infection. Under wartime or mass-casualty conditions, however, there may be an inadequate supply of these agents. This study aimed to identify those patients most likely to benefit therefrom.**

Methods: **Logistical regression analysis of data from the U.S. Army Burn Center was performed. Mortality data for the period immediately preceding the introduction of topical mafenide acetate (MA) (1950–1963) were compared with data for the subsequent period (1964–1968). During the second period, MA was routinely applied but treatment was otherwise similar. The mortality decrement attributed to MA was determined for various ages and burn sizes.**

Results: **For patients of combatant age (20–50 years), MA was associated with a greater than 10% reduction in mortality for those with burns of 40–79% of the total body surface area (TBSA). Only a minimal effect on mortality was noted for those patients with burns smaller than 40% or greater than 79%.**

Conclusions: **When resources are limited, topical therapy (specifically, MA) is likely to confer the greatest survival benefit for combatants with burns of 40–79% TBSA.**

Key Words: **Burns, Wound infection, Survival rate, Mafenide, Disaster planning, Military medicine.**

J Trauma. 2004;56:863–866.

During non-nuclear conflict, it is estimated that burns will comprise 5–20% of combat injuries, depending on the scenario.[1] Mass burn casualties present logistical problems for health care professionals. During wartime or after large-scale civilian disasters, mass casualties with burn injuries place considerable strain on logistical elements of command structures, including provision of medical supplies. Furthermore, given that the tactical situation will dictate the rate at which burn casualties are evacuated from the theater of operations, it is probable that burned soldiers will take longer to arrive at a burn center than similarly injured civilians. Failure to employ effective topical antimicrobial agents during this prolonged evacuation places burned soldiers at risk of life-threatening invasive burn wound infection (previously known as burn wound sepsis).

Topical antimicrobial agents are bulky and heavy to transport, such that their availability in combat zones may be limited, yet current standard operating procedures require application of topical antimicrobial cream to all burn wounds.[2] This study aimed to ascertain which burn patients will derive most benefit from application of topical antimicrobial agents and to provide appropriate guidance for triage officers.

A reduction in the incidence of invasive burn wound infection and accompanying mortality, after the introduction of topical mafenide acetate in 1964, previously has been reported from this center.[3,4] During the period 1962–1963, there were 290 admissions, 111 deaths, and 65 deaths with invasive burn wound infection; then during 1964–1966, there were 630 admissions, 129 deaths, and 13 deaths with invasive burn wound infection.[3] In that study, however, the independent effects of burn size and age on mortality were not ascertained. In the present study, therefore, we have employed logistical regression analysis to account for these effects across the continuum of ages and burn sizes.[5]

MATERIALS AND METHODS

This study was a retrospective analysis of an existing institutional database. It was reviewed by the Institutional Review Board, which determined that it was exempt from approval, in accordance with applicable Department of Defense and NIH guidelines. The U.S. Army Institute of Surgical Research (the U.S. Army Burn Center) has been collecting data relating to mortality of burn patients since 1950. Furthermore, the senior author (ADM) has been continuously associated with the Institute since 1954. No topical antimicrobial therapy was used during the period 1950–1963. Burn wounds were treated by the exposure method, with daily hydrotherapy and debridement until the wounds healed or were replaced with a bed of granulation

Submitted for publication September 7, 2002.
Accepted for publication October 16, 2002.

From The Burns Unit (T.P.LaH.B.), Middlemore Hospital, Auckland, New Zealand, and the U.S. Army Institute of Surgical Research (L.C.C., A.D.M., A.T.M.), Fort Sam Houston, Texas.
Presented at the Australia New Zealand Burn Association Annual Scientific Meeting 2002, October 22, 2002, Auckland, New Zealand.

Funded, in part, by the Combat Casualty Care program of the U.S. Army Medical Research and Materiel Command, Fort Detrick, MD.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Address for reprints: Library Branch, U.S. Army Institute of Surgical Research, Bldg. 3611, 3400 Rawley E. Chambers Ave., Fort Sam Houston, TX 78234-6315.

DOI: 10.1097/01.TA.0000044565.69410.95

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 APR 2004	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Survival benefit conferred by topical antimicrobial preparations in burn patients: a historical perspective	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Brown T. P., Cancio L. C., McManus A. T., Mason Jr. A. D.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**4**	

tissue sufficient to accept a partial thickness skin graft.[3] With the widespread use of penicillin in the 1950s, streptococcal wound infection came under control and was replaced by invasive gram-negative burn wound infection as the leading cause of death in burn patients.[6–10] Mafenide acetate, an effective topical agent against gram-negative burn wound infection, was introduced in 1964 and was the sole topical antimicrobial agent employed between 1964 and 1968. Care did not otherwise change significantly at this burn center during the period 1964–1968. Beginning in 1969, exposure therapy gradually gave way to early excision and grafting of deep burns, a procedure previously limited to a few experimental studies.[11–13] In addition, some strains of *Providencia* developed resistance to mafenide acetate, which was associated with an increase in invasive burn wound infection and in mortality.[5] Likewise, there was a significant increase in sepsis secondary to *Pseudomonas* bacteremia during 1969–1973.[14] Silver sulfadiazine was added to the topical regimen in 1973. Thus, consistency in treatment regimens permits comparison of data from the pre-mafenide period (1950–1963) with data from the period during which mafenide was routinely employed, but before the *Providencia* outbreak (1964–1968).

Data including year of injury, age, TBSA, and mortality were obtained from the existing database of the U.S. Army Burn Center. Patients admitted to the Center after the second postburn day also were excluded, as records relating to topical therapy they may have received were unreliable. Patients admitted for injuries caused by processes other than flame or scald, such as electric or chemical injury, also were excluded. All other patients were included, regardless of burn size or age. Multiple logistic regression analysis (SPSS, version 10.1, Chicago, IL) was undertaken, entering each patient as an individual data point.

RESULTS

During 1950–1963 there were 1515 admissions to the burn center, of whom 842 met the inclusion criteria; 599 (71%) of these lived. During 1964–1968 there were 1430 admissions, of whom 488 met the inclusion criteria; 353 (72%) of these lived. Data analysis is based on the 842 cases for 1950–1963 and the 488 cases for 1964–1968. Logistic regression of the data for both time periods with respect to burn size and patient age is described by the equation:

$$L = a_1 + a_2(\text{TBSA}) - a_3(\text{age}) + a_4(\text{age}^2/100) - a_5(\text{age}^3/10000)$$

$$p = e^L/1+e^L$$

L = logistic of % mortality

p = expected fractional mortality

The values for the variables during both time periods are given in Table 1.

A three dimensional "plane" describing the probability of mortality and its relationship to age and burn size was generated for both time periods (Figs. 1 and 2). As little else had changed in the therapeutic management of patients during the two time periods, subtraction of one plane from the other produces a third plane that can be considered to represent the percentage difference in mortality resulting from adoption of topical mafenide acetate (Fig. 3). The decrease in mortality of patients for selected burn sizes in the combatant age range (20–50 years) is shown in Table 2.

Table 1 Variables Resulting From Logistic Regression of Mortality Data

Variable	1950–1963	1964–1968
a_1	−3.8241	−4.9886
a_2	0.1133	0.1003
a_3	0.2324	0.1292
a_4	0.7323	0.4312
a_5	0.5388	0.2387

These variables were derived from logistic regression analysis of actual patient data for the periods shown. In conjunction with the equation (see text), the predicted mortality for a patient with a given age and burn size can be estimated.

DISCUSSION

Under ideal circumstances, combatants would receive treatment equivalent in quality to the care they would receive in a civilian environment. However, tactical and logistical constraints in the theater of operations may make this impossible, producing a higher mortality rate in war.[15] In view of this, the 1979 NATO Defense Research Group concluded that burns over 40% TBSA are "beyond the scope of therapeutic capabilities in times of crisis," and therefore are triaged as "expectant."[16] This conclusion, by current standards, requires revision: the lethal-area 50% (LA_{50}) for 21-year-old patients

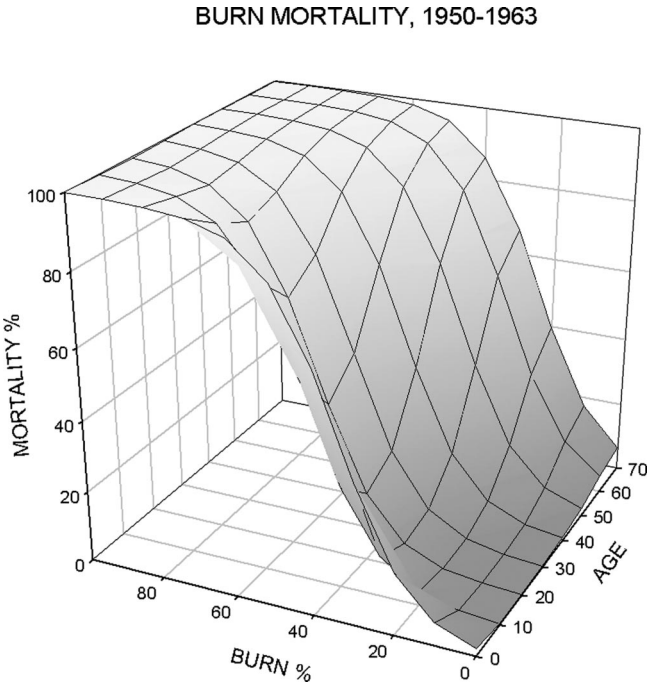

Fig. 1. *Three-dimensional plane depicting the relationship of TBSA, age, and mortality for study patients, 1950–1963.*

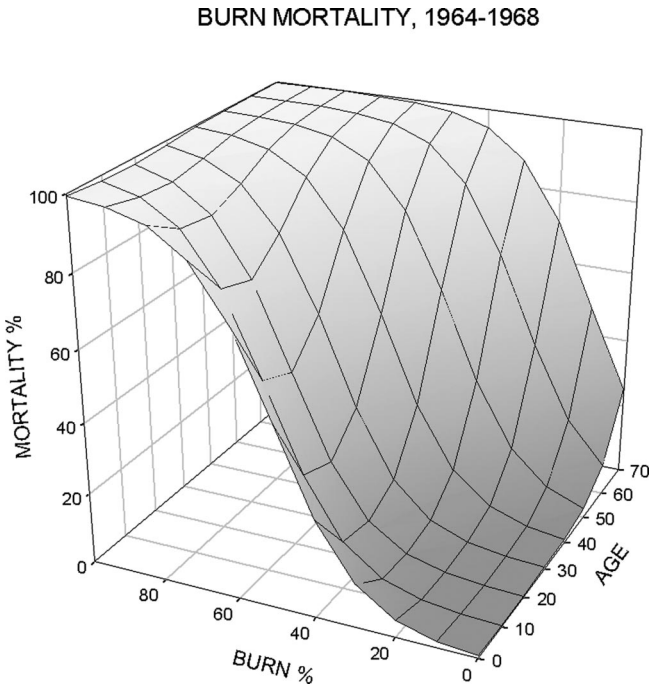

Fig. 2. *Three-dimensional plane depicting the relationship of TBSA, age, and mortality for study patients, 1964–1968.*

with burns treated at the U.S. Army Burn Center is now 82%.[17] The majority of combatants therefore fall into a group with a 50% chance of survival after a burn of approximately

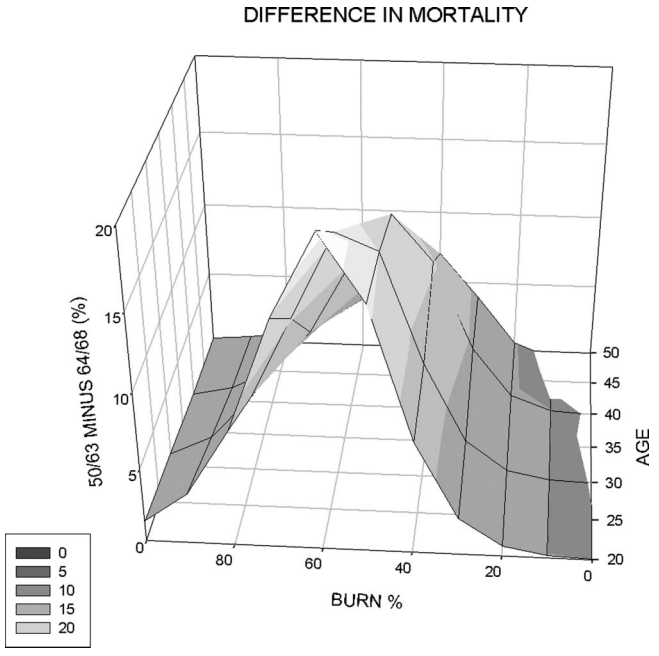

Fig. 3. *Three-dimensional plane, obtained by subtracting the plane in Figure 2 from the plane in Figure 1, depicting the observed improvement in mortality between the two periods. For clarity, the graph is limited to the 20- to 50-year-old age range. Note the greatest improvement is noted for patients 20 years of age with burns mid-range in size.*

Table 2 Relative Percentage Decrease in Mortality for Burn Patients of Combatant Age Treated with Topical Mafenide Acetate

TBSA, %	Age, years			
	20	30	40	50
10	0	0	0	0
20	1	1	1	1
30	2	3	4	4
40	7	8	10	7
50	16	15	14	6
60	20	16	10	3
70	15	11	5	2
80	8	5	2	1

This table gives the difference in predicted mortality, obtained using the logistic regression equation (see text), for patients with the ages and burn sizes shown. Note that the greatest survival benefit occurred for 20-year-old patients at the midrange of burn size. These results are based on discrete ages and burn sizes, not ranges. The exact mortality difference for a given age and burn size should not be extrapolated from this table, but should be predicted by applying the logistic equation.

82% TBSA under peacetime conditions. Thus, it would be entirely appropriate to resuscitate combat casualties with burns corresponding to this LA_{50}—except in mass casualty situations in which limited resources are overwhelmed by the number of patients. In such situations, the upper triage limit should be lowered in 10% increments until the available supplies match patient needs.[2]

Resuscitation of patients with large burns places constraints on medical supplies, and the use of topical antimicrobials is known to confer significant survival benefit in a proportion of patients.[3] In the present study, the incremental beneficial effect of mafenide acetate on mortality decreased below 10% in patients with burns of less than 40% or greater than 79% TBSA and was maximal for young patients with burns of 60%. These data reinforce two concepts: that patients with small burns usually survive and that patients with the largest burns usually die, regardless of interventions such as the topical application of antimicrobials. Invasive gram-negative infection of very small or of very large burns does not appear to contribute significantly to mortality.

In the United States and the United Kingdom, silver sulfadiazine cream is the most commonly used topical preparation. There is a documented spectrum of resistance,[14] which includes nearly all *Enterobacter cloacae* and certain *Pseudomonas* strains.[18] Moreover, it is effective only when applied soon after an injury, having no effect on established infection. Although effective against *Candida* sp., silver sulfadiazine has no efficacy against the true fungi, which continue to cause invasive infection in a small percentage of burn patients.

Mafenide acetate, most commonly applied as an 11.1% cream (Sulfamylon®, Bertek Pharmaceuticals Inc., Sugar Land, TX), has a proven track record in wartime burn management.[2] It has the advantages of limited antimicrobial resistance and an ability to penetrate burn eschar, making it effective against established invasive burn wound infection.

There is up to a 7% incidence of hypersensitivity, most commonly manifested by a rash,[2] and it causes discomfort on application to partial thickness injuries. When used twice daily as the only topical antimicrobial in patients with large burns, mafenide acetate may cause metabolic acidosis secondary to carbonic anhydrase inhibition, which can present problems in patients with respiratory failure.[19] Like silver sulfadiazine, it has no antifungal activity. When used as an 11.1% cream in a water-miscible base, it acts as a constant-release preparation, which must be replaced every 12 hours (and more often as needed).[20] We estimate that approximately 20 g of mafenide acetate cream is required per percent burn per 24 hours. At the U.S. Army Burn Center, mafenide acetate and silver sulfadiazine creams currently are alternated twice daily to minimize the side effects while realizing the benefits of these two agents.

There are limitations to the present study. Although no significant change in therapy is thought to have occurred in 1964 other than the introduction of topical chemotherapy, it is possible that other unrecognized factors may have contributed to the reduction in mortality. Even so, this reduction was so remarkable to providers at the time that no randomized, prospective trial was deemed to be ethically or operationally feasible. There is indirect evidence that topical mafenide was responsible for the reduction in mortality during 1964–1968, in the burn-wound microbiology of the following years. Shortly after 1969, a strain of *Providencia* that was resistant to mafenide became prevalent in this burn center, and mortality increased to pre-1964 levels.[5] Once this strain was eradicated, mortality returned to that of 1964–1968, implying that topical therapy produced the most dominant effect on mortality. Invasive burn wound infection was poorly understood until 1964,[21,22] such that its actual incidence during the study period is impossible to determine with certainty. However, as our endpoint was death rather than local wound infection, we feel that this observation does not compromise the validity of our conclusions.

Caution should be exercised in applying the conclusions of this historical study to present-day practice. These results do not define the relative effect of topical antimicrobials on patients in whom all the other advances in modern burn care are applied or their relative effect in a combat environment. We would, therefore, not recommend that planners utilize these data to limit the supply of topical antimicrobials intended for use during military operations or peacetime disasters. Rather, we consider that they are most applicable to overwhelming mass-casualty events.

CONCLUSIONS

When faced with overwhelming numbers of burn patients and a delay in transportation to a specialized burn center, a judgment must be made as to which patients will benefit the most from topical antimicrobial therapy. Based on logistic regression analysis of data for 1950–1968, the incremental mortality benefit attributed to topical antimicrobial therapy was determined. For patients of combatant age (20–50 years old), this benefit was greatest for those with burns of 40–79% TBSA. We hope that the data provided by this study will be of assistance to those tasked with making difficult decisions in the event of limited resources and mass burn casualties.

REFERENCES

1. Sparkes BG. Treating mass burns in warfare, disaster or terrorist strikes. *Burns.* 1997;23:238–247.
2. Bowen TE, Bellamy RF. *Emergency War Surgery Second United States Revision of the Emergency War Surgery NATO Handbook.* Washington, DC: US Government Printing Office; 1988.
3. Pruitt BA Jr, O'Neill JA Jr, Moncrief JA, Lindberg RB. Successful control of burn-wound sepsis. *JAMA.* 1968;203:1054–1056.
4. Lindberg RB, Moncrief JA, Mason AD Jr. Control of experimental and clinical burn wound sepsis by topical application of sulfamylon compounds. *Ann NY Acad Sci.* 1968;150:950–960.
5. Pruitt BA, Mason AD Jr. Epidemiological, demographic and outcome characteristics of burn injury. In: Herndon DN, ed. *Total Burn Care.* London: W.B. Saunders; 1996:5–15.
6. Goodwin CW, Yurt RW. Epidemiology of burn wounds. In: Davis JM, Shires GT, eds. *Host Defenses in Trauma and Surgery.* New York: Raven Press; 1986:5–18.
7. Liedberg NC, Reiss E, Artz CP. Infection in burns. III. Septicemia, a common cause of death. *Surg Gynecol Obstet.* 1954;99:151–158.
8. Artz CP, Teschan PE. Infection—a major unresolved problem in severe trauma. *Am J Surg.* 1957;93:647–53.
9. Tumbusch WT, Vogel EH, Butkiewicz JV, Graber CD, Larson DL, Mitchel ET. Septicemia in burn injury. *J Trauma.* 1961;1:22–31.
10. Rabin ER, Graber CD, Vogel EH, Finkelstein RA, Tumbusch WA. Fatal pseudomonas infection in burned patients. *N Engl J Med.* 1961;265:1225–1231.
11. MacMillan BG, Artz CP. A planned evaluation of early excision of more than twenty-five per cent of the body surface in burns. *Surg Forum.* 1956;7:88–93.
12. Switzer WE, Jones JW, Moncrief JA. Evaluation of early excision of burns in children. *J Trauma.* 1965;5:540–546.
13. Taylor PH, Moncrief JA, Pugsley LQ, Rose LR, Switzer WE. The management of extensively burned patients by staged excision. *Surg Gynecol Obstet.* 1962;115:347–352.
14. McManus AT, Mason AD Jr, McManus WF, Pruitt BA Jr. Twenty-five year review of Pseudomonas aeruginosa bacteremia in a burn center. *Eur J Clin Microbiol.* 1985;4:219–223.
15. Scott R. Munich workshop on epidemiology, triage and treatment of military burn patients. Defense Research Group 11, Panel VIII, Annual Report: NATO AC/243 (Panel VIII/RSG.11)D/3, 1985.
16. Crocq L, Doucet J. Physiopathology of serious burn cases. Defence Research Group 9, Panel VIII: NATO AC/243 (Panel VIII/RSG.9)D/26, 1979.
17. Pruitt BA Jr. Centennial changes in surgical care and research. *Ann Surg.* 2000;232:287–301.
18. Pruitt BA Jr, Goodwin CW, Cioffi WG. Thermal injuries. In: Davis JH, Sheldon GF, eds. *Surgery A Problem-Solving Approach.* St. Louis: Mosby; 1995:643–720.
19. White MG, Asch MJ. Acid-base effects of topical mafenide acetate in the burned patient. *N Engl J Med.* 1971;284:1281–1286.
20. Harrison HN, Bales H, Jacoby F. The behavior of mafenide acetate as a basis for its clinical use. *Arch Surg.* 1971;103:449–453.
21. Teplitz C, Davis D, Mason AD Jr, Moncrief JA. Pseudomonas burn wound sepsis. I. Pathogenesis of experimental pseudomonas burn wound sepsis. *J Surg Res.* 1964;4:200–216.
22. Teplitz C, Davis D, Walker HL, Raulston GL, Mason AD Jr, Moncrief JA. Pseudomonas burn wound sepsis: II. Hematogenous infection at the junction of the burn wound and the unburned hypodermis. *J Surg Res.* 1964;4:217–222.